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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,035	02/09/2001	Tariq Ghayer	BBC-084	8433

7590 11/20/2003

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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,035	GHAYER ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003 and 20 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12,14-38,44-46 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-12,14-38,44-46 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/03 has been entered.

2. Applicant's amendment, filed 4/21/03, has been entered.
   Claims cancelled: 1-3, 13, 39-43 and 47-60.
   Claims currently amended: 22.
   Claims pending: 4-12, 14-38, 44-46 and 61.

Claims 4-12, 14-38, 44-46 and 61 *are under consideration in the instant application.*

3. This Office Action will be in response to applicant's arguments, filed 4/21/03 . The rejections of record can be found in the previous Office Action.

It is noted that New Grounds of Rejection are set forth herein.

Claim Rejections - 35 USC § 112 first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant's arguments, filed 4/21/03, have been fully considered but have not been found persuasive, essentially for the reasons of record, which are incorporated herein by reference as if set forth in full.

Applicant argues that the specification provides adequate written description of the claims as amended. Applicant's arguments are essentially the same as those of record and focus on the fact that there are examples in the art in which not all six CDRs are required for binding to the antigen of interest.

The claims as amended are drawn to any antibody that comprises at least one variable region capable of binding an epitope of human IL-18 (independent claim 22 and claims dependent therefrom), or that comprises fewer than six CDRs of defined sequence (independent claims 29-31 and 36-38).

However, there is no requirement that the antibodies formed from these subcomponents bind human IL-18; rather, the only requirement is that the subcomponents come from an antibody that binds human IL-18. Neither is there sufficient evidence in the disclosure that any given CDR or variable region is sufficient structure to provide the function of binding human IL-18.

The Examiner acknowledges that there are examples in the art in which the specificity of the antibody is determined by fewer than all six CDRs. However, instances in which specificity is determined by fewer than all six CDRs are the exception. Applicant does not appear to provide adequate support that the disclosed antibodies differ from the majority of antibodies and do not require all six CDRs in the context of an antibody framework. Since Applicant has not provided a common structure which defines the function of IL-18 binding, the essential feature of the instant invention, the Examiner maintains that the ordinary artisan would not recognize Applicant to be in possession of the instantly claimed genus of antibodies.

Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

The amendment does not obviate the rejection of record; the rejection is therefore maintained.

6. Claims 22-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies and antigen-binding fragments thereof in which the three CDRs in the heavy chain variable region and the three CDRs in the light chain variable region are all defined by a single antibody and which bind the relevant antigen (human IL-18 or a peptide epitope thereof) and for mutants of these antibodies in which a limited number of defined changes are made in one or more CDRs; does not reasonably provide enablement for antibodies and antigen-binding fragments thereof that comprise less than three heavy chain CDRs and three light chain CDRs defined by the amino acid sequence of a parental antibody that binds the same antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 4/21/03, have been fully considered but have not been found persuasive, essentially for the reasons of record.

The rejection of record is incorporated herein as if re-iterated in full. Applicant's arguments are addressed below.

The breadth of the claims as amended encompasses any antibody that comprises at least one variable region capable of binding an epitope of human IL-18 (independent claim 22 and claims dependent therefrom), or that comprises fewer than six CDRs of defined sequence (independent claims 29-31 and 36-38).

Applicant argues that the skilled artisan recognized that single variable regions were sufficient to support antigen binding, noting that human VH domains can be "camelised" and single domain antibodies were known in the art. Applicant concludes that because the art provides an example in which fewer than six CDRs can form an antigen-binding compound, the instant specification is enabling.

The Examiner does not dispute that some human VHs can bind camelised and that single domain antibodies can be made. However, at issue is whether they can be made from the anti-human IL-18 antibodies disclosed in the specification without undue experimentation given the guidance provided in the instant specification. Applicant relies on specific examples but does not establish that these examples are relevant to the disclosed antibodies. For example, camelisation of human VH domains requires an antibody in which the VL interface is amenable to mutation and which has CDRs that form large protruding loops (Riechmann and Muyldermans J. Immunol. Meth. 1999; 231:25-38, see especially page 29 at the bridging paragraph and pages 34-35 "9. Special features of single domain antibodies"). There does not appear to be sufficient guidance regarding the disclosed antibodies and the application of the methodology of the examples in the art upon which Applicant relies.

Further, there is no requirement that the antibodies formed from these subcomponents bind human IL-18; rather, the only requirement is that the subcomponents come from an antibody that binds human IL-18. The specification does not provide sufficient guidance as to how the skilled artisan should use an antibody that does not have the ability to bind human IL-18.

The specification as filed provides no working examples showing that fewer than all six CDRs are sufficient for binding to IL-18 or an epitope thereof. Neither does the specification appear to provide sufficient guidance as to which subsets of CDRs could be used in an antibody comprising less than all six CDRs from an antibody having IL-18 binding specificity and still maintain IL-18 binding. Without sufficient guidance, it would require undue experimentation of the skilled artisan to make antibodies or antigen-binding fragments thereof which could bind IL-18 and be used in methods of inhibiting IL-18 function that comprised fewer than all six CDRs from a parental antibody that bound IL-18.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Given the recognized unpredictable nature of making antibodies with a desired specificity having fewer than all six CDRs from a reference antibody and the lack of sufficient guidance provided in the specification; the Examiner maintains that the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

The rejection is maintained.

Claim Rejections – 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 4-12, 14-24, 44-46 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al. (US Pat No. 6,075,181, of record) and Dinarello et al. (J. Leukoc. Biol. 1998; 63:658-664, IDS #A4).

Applicant's arguments, filed 4/21/03, have been fully considered but have not been found convincing. Applicant's arguments are addressed in the context of the reiteration of the rejection of record, as applied to the amended claims.

The instant claims are generally drawn to human antibodies to human IL-18 having various functional properties in terms of their binding to IL-18.

As previously noted, Kucherlapati et al. teach a method of producing fully human monoclonal antibodies to any protein of interest, but especially cytokines, by using the protein to immunize mice which express human antibody genes (see entire document, but especially columns 8-9. Kucherlapati et al. teach that fully human monoclonal antibodies are highly advantageous compared to rodent antibodies or even humanized antibodies for therapeutic applications, because administration of human antibodies to humans avoids the undesired immune responses elicited by administering non-human antibodies to humans (see column 8, especially lines 21-41).

Kucherlapati et al. also teach that the human antibody genes can be cloned and used to produce recombinant, fully human, monoclonal antibodies, e.g., for phage display libraries (e.g., columns 6-7). Kucherlapati et al. teach that such recombinant human antibodies offer the advantage that phage libraries can be screened for selection of antibodies with the highest affinity to the antigen of interest, or can be manipulated to increase the affinity of the antibody for the antigen (e.g., column 7, especially the comment at lines 58-65).

Kucherlapati et al. do not teach human antibodies to IL-18.

Dinarello et al. teach that human IL-18 had been cloned and produced recombinantly (see e.g. page 659 "Molecular cloning of IGIF"). Dinarello et al. review that IL-18 initiates the Th1 inflammatory cytokine cascade, leading to the production of later cytokine mediators such as TNF-α, IL-1 and IL-8, and that antibodies to IL-18 can inhibit the in vivo production of other cytokines such as TNF-α (e.g. page 660, right column). Dinarello et al. note that given what is known about the role of cytokines such as TNF-α, IL-1 and IL-8 that are induced by IL-18 in human disease such as rheumatoid arthritis and Crohn's Disease; that preventing the activity of IL-18 which induces these other cytokines is a sensible clinical strategy (e.g., page 662 "What is the clinical importance of the pro-inflammatory cytokine IL-18?). Dinarello et al. also note in this discussion of the clinical importance of inhibiting IL-18 activity that neutralizing anti-IL-18 antibodies are a therapeutic option for inhibiting IL-18 activity.

Applicant argues that the references neither singularly or in combination teach or suggest fully human antibodies to human IL-18 and that the Examiner has employed improper hindsight reconstruction. Applicant further argues that there was no reasonable expectation that the references could be successfully combined.

The Examiner maintains that it would have been obvious to the ordinary artisan at the time the invention was made to produce human antibodies to human IL-18 that were capable of neutralizing the activity of IL-18. Recombinant IL-18 was known in the art at the time the invention was made, as taught by Dinarello et al. Kucherlapati et al. provide a method of producing fully human antibodies to human cytokines. Thus as noted previously the ordinary artisan at the time the invention was made would have had a reasonable expectation that, given the availability of recombinant human IL-18, fully human antibodies to human IL-18 could be produced using the method of Kucherlapati et al.

As also noted previously, the ordinary artisan at the time the invention was made would have been motivated to produce fully human monoclonal antibodies that could bind to and neutralize human IL-18 in order to provide a therapeutic reagent that could be administered to humans without eliciting the undesirable immune responses associated with the administration of rodent or even humanized rodent antibodies, as taught by Kucherlapati et al. The desirability of neutralizing antibodies to human IL-18 is clearly taught by Dinarello et al.

Further, the ordinary artisan at the time the invention was made would have been motivated to provide recombinant forms of the fully human antibodies so that the binding affinity and ability of the antibody to neutralize human IL-18 could be improved by successive rounds of manipulation and screening of phage display libraries of the human anit-IL-18 monoclonal antibodies. Although monoclonal antibodies typically have k_{off} rate constants as measured by surface plasmon resonance and inhibition activity with an IC_{50} in the ranges recited, using the affinity maturation approach as taught by Kucherlapati et al would have ensured that the ordinary artisan would have obtained human antibodies that bound human IL-18 and had k_{off} rate constants of $1x10^{-6}s^{-1}$ and IC_{50} values of $1x10^{-11}M$. Further, the affinity modifications taught by Kucherlapati et al. would have resulted in at least one amino acid substitution or insertion that improves the IL-18 binding as compared to the original antibody. Any human anti-human IL-18 antibody would of necessity possess at least one variable region CDR domain capable of binding an epitope of human IL-18, and would bind an epitope of human IL-18 comprising SEQ ID NOS:3, SEQ ID NO:33, SEQ ID NO:70 or SEQ ID NO:71 since SEQ ID NOS:3, 33, 70 and 71 are each subsequences of human IL-18.

Finally, given that the ordinary artisan would have been motivated to provide human monoclonal antibodies to human IL-18 because of their therapeutic potential in inflammatory diseases, as taught by Dinarello et al.; the ordinary artisan would have clearly been motivated to formulate the human anti-human IL-18 antibody in a pharmaceutical composition. The addition of at least one additional therapeutic agent already shown to have some efficacy against these inflammatory diseases, e.g., the addition of methotrexate or anti-TNFα for the treatment of rheumatoid arthritis, would have also been an obvious combination at the time the invention was made to provide a more efficacious therapeutic composition.

While Applicant's Remarks, filed 4/21/03 regarding the failure of Dinarello et al. to teach human antibodies are again acknowledged, the Examiner maintains that the combination of Dinarello et al. and Kucherlapati et al. provide both the motivation to produce human antibodies to human IL-18 and a reasonable expectation of successfully producing human anti-human IL-18 antibodies. The amendment to claim 22 does not alter the rejection of record. Therefore, the Examiner maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record, as applied to the amended claims, is maintained.

Conclusion

9. No claim is allowed.

10. It is again noted that claims drawn to the following anti-IL-18 antibodies would appear to be free of the art:
1) an antibody comprising the heavy chain variable region defined by SEQ ID NO:18 and the light chain variable region defined by SEQ ID NO:19;
2) an antibody comprising the heavy chain variable region defined by SEQ ID NO:28 and the light chain variable region defined by SEQ ID NO:29;
3) an antibody comprising a heavy chain variable region in which the CDRs are defined by SEQ ID NOS:9-11 and a light chain variable region in which the CDRs are defined by SEQ ID NOS:12-14; and
4) an antibody comprising a heavy chain variable region in which the CDRs are defined by SEQ ID NOS:20-22 and a light chain variable region in which the CDRs are defined by SEQ ID NOS:23-25.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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November 14, 2003

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